EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

SATRALIZUMAB IS INDICATED AS A MONOTHERAPY OR IN COMBINATION WITH IMMUNOSUPPRESSIVE THERAPY (IST) FOR THE TREATMENT OF NEUROMYELITIS OPTICA SPECTRUM DISORDERS (NMOSD) IN PATIENTS FROM 12 YEARS OF AGE WHO ARE ANTI-AQUAPORIN-4-IGG SEROPOSITIVE

Project ID: PTJA13
Project Plan

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V0.1	**11/11/2019**	PICO description including background and incorporation of PICO survey results
V0.2	**04/12/2019**	Incorporation of dedicated reviewer comments
V0.3	**05/05/2020**	Updated sections 3.3.1. and 3.3.2.
V1.0	**28/04/2021**	Final Project Plan

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For further information on the work distribution and further contributors, please see section 4.1.

Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse event
AQP4	Aquaporin-4
AQP4-IgG	Aquaporin-4 antibodies
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous system
CSF	Cerebrospinal fluid
CSR	Clinical Study Reports
DOI	Declaration of Interest
EDSS	Expanded Disability Status Scale
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
HRQoL	Health-related quality of life
HTAi	Health Technology Assessment international
IL-6	Interleukin 6
IL-6R	Interleukin 6 receptor
IST	Immunosuppressive therapy
mAb	Monoclonal antibody
MOG	Myelin oligodendrocyte glycoprotein
MOG-Ab	Antibody against MOG
MRI	Magnetic resonance imaging
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis Optica Spectrum Disorders
PICO	Population, intervention, control, outcome
pMAH	Prospective Marketing Authorisation Holder
Th17	T helper 17 cells

1 INTRODUCTION

On 20-08-2019, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of satralizumab (*Roche*) agreed that EUnetHTA will perform a joint relative effectiveness assessment of satralizumab, which is indicated as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive.

On 22-04-2021 satralizumab was granted positive CHMP opinion. This means that the finalization of the PTJA13 assessment would occur after the closure of EUnetHTA Joint Action 3. Due to this, the authoring team was unable to continue the assessment. Although the assessment will not be continued by EUnetHTA, the marketing authorization is pending decision by the European Commission, and therefore satralizumab will be assessed through national HTA procedures in due time. The authoring team of PTJA13 has finalized the project plan, outlining EUnetHTA's PICO proposal which has been adapted following the CHMP opinion and would have been considered for this assessment should it have continued

1.1 Background

Neuromyelitis optica spectrum disorders (NMOSD) are rare inflammatory diseases of the central nervous system that are caused by astrocyte injury and secondary demyelination (1). NMOSD were previously considered to be a variant of multiple sclerosis, however the identification of aquaporin-4 antibodies (AQP4-IgG) in the serum of these patients led to the consideration that it would be a distinct entity. Aquaporin-4 (AQP4), the target antigen of NMOSD is a water channel protein highly concentrated in spinal cord grey matter, periaqueductal and periventricular regions, and astrocytic foot processes at the blood-brain barrier. AQP4-IgG are now known to be pathogenic. Their detection in serum provides moderate sensitivity and high specificity for the diagnosis of NMOSD. AQP4-IgG are produced in the periphery and enter the central nervous system where they attach to astrocytes, inducing complement-mediated cell damage, granulocyte infiltration and astrocyte death. Astrocyte death further leads to secondary oligodendrocyte death, demyelination and neuronal cell death. Approximately 80% of patients with NMOSD have AQP4-IgG (seropositive NMOSD). Another possible antigenic candidate is myelin oligodendrocyte glycoprotein (MOG), a minor myelin component exclusively expressed on the surface of myelin sheaths in the central nervous system. The antibody against MOG (MOG-Ab) is found in 4–11% of NMOSD patients and does not co-occur with AQP4-IgG seropositivity (1).

NMOSD prevalence ranges from 0.5 to 10 per 100,000 people (2,3). The incidence of this disorder is higher in women (2.8:1) (2). The median age of onset is 39 years old (2,3).

NMOSD can clinically manifest as acute, recurrent attacks of optic neuritis that can be complicated by vision loss, longitudinally extensive transverse myelitis (characterized by symmetric paraparesis or quadriparesis, bladder dysfunction, and sensory loss below the level of the spinal cord lesion) or syndromes of the area postrema that include intractable hiccups or nausea/vomiting. Brainstem involvement may lead to acute neurogenic respiratory failure and death (4).

Attacks are characterized by neurological deficits that develop over days with variable resolution during the following months leading to progressive disability (4). The large majority of patients (90%) have recurrent disease with relapses that occur at unpredictable intervals. The natural history of NMOSD is of stepwise deterioration due to accumulation of visual, motor, sensory, and bladder deficits from recurrent attacks. Long-term disability and mortality rates are high (1).

Exams that are done to evaluate patients with NMOSD include: serologic testing for AQP4-IgG, brain and spine imaging with magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis and ophthalmologic evaluation (4).

Revised consensus criteria published in 2015 base the diagnosis of NMOSD on the presence of core clinical characteristics, AQP4-IgG status and MRI features (5).

1.2 The technology

Satralizumab is a humanized recombinant monoclonal antibody (mAb) targeting the IL-6 receptor (IL-6R) with immunomodulatory potential (6). IL-6 is a pro-inflammatory pleiotropic cytokine produced by a large number of cell types, including T and B cells, monocytes and fibroblasts. It participates in various physiological processes, such as T-cell activation, induction of immunoglobulin secretion, and induction of hepatic protein synthesis in the acute phase of inflammation. In NMO, IL-6 promotes the differentiation of inflammatory Th17 cells and plasmablasts inducing production of pathogenic antibodies. It also increases blood–central nervous system (CNS) barrier permeability, allowing infiltration of antibodies and pro-inflammatory cells into the CNS. Satralizumab specifically binds to soluble and membrane receptors for IL-6 and inhibits their signal transmission. The constant and variable regions of satralizumab were engineered to give the molecule longer plasma half-life (6).

1.3 Current clinical management

Current treatments used for NMOSD include immunosuppression with high-dose steroids or plasmapheresis for the treatment of steroid-unresponsive patients during acute relapses and long-term immunosuppression to prevent further relapses (7). The goals of long-term immunosuppression include: delaying time to relapse, reduction of severity of future attacks and minimization of permanent disability.

Long-term immunosuppressive agents used in this context include rituximab, azathioprine, mitoxantrone, mycophenolate mofetil and cyclophosphamide. The evidence for their utilization results from observational studies. They are sometimes used in combination with prednisolone. Several open-label, uncontrolled and non-randomized studies showed reduction in relapse rate and disability after treatment with these immunosuppressive agents (8).

- Rituximab is a chimeric anti-CD20 monoclonal antibody capable of depleting mature and precursor B cells (9).
- Azathioprine is a purine synthesis inhibitor and interferes with the proliferation of cells, especially leucocytes (10).
- Mitoxantrone is an anthracenedione antineoplastic agent that intercalates with DNA and inhibits both DNA and RNA synthesis, suppressing T-cell and B-cell immunity (12).
- Mycophenolate mofetil is a prodrug of mycophenolic acid, and classified as a reversible inhibitor of inosine monophosphate dehydrogenase. This is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides. T- and B-lymphocytes are more dependent on this pathway than other cell types (13).
- Cyclophosphamide is an alkylating chemotherapeutic drug related to nitrogen mustards and a non-specific immunosuppressant that affects both T-cell and B-cell functions. Immunosuppression is transient when cyclophosphamide is given in standard pulse doses, and the immune system returns to baseline within a few months to a year after cessation (11).
- Tocilizumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody (14).

In August 2019, the first clinical trial performed in patients with NMOSD was published (15). It was a randomized, double blind trial, where 143 adults were randomly assigned in a 2:1 ratio to intravenous eculizumab or matched placebo with time to event outcomes. The continued use of stable-dose IST was permitted. Eculizumab is an anti-complement-5 antibody. Among patients with AQP4-IgG-positive NMOSD, those who received eculizumab had a significantly lower risk of relapse than those who received placebo. There was no significant between-group difference in measures of disability progression. Eculizumab is the only licensed treatment for NMOSD in patients who are anti-aquaporin-4 antibody-positive, all the others are used off-label (16).

The European Academy of Neurology's guidelines for the treatment of NMO patients published in 2010 state that long-term treatment options should be initiated as soon as the diagnosis of NMO is made (7). Seronegative NMOSD should be treated in the same way as seropositive NMOSD. Data favouring specific therapies are weak. Immunosuppression is the preferred treatment. The same guidelines consider that either rituximab or azathioprine plus prednisolone can be used as first line therapies.

Cyclophosphamide or mitoxantrone or mycophenolate mofetil can be considered as second line treatments.

In 2012, a group of NMOSD experts published a set of recommendation practices taking into account retrospective and prospective series of off-label use of various immunosuppressant in different countries. They recommended azathioprine, mycophenolate mofetil, rituximab and prednisone as first line agents in NMOSD (17).

In 2014, The Neuromyelitis Optica Study Group composed of German neurologists from university and academic teaching hospitals, suggested azathioprine and rituximab as first-line treatments, methotrexate, mycophenolate mofetil and mitoxantrone, were recommended as second-line treatments (18).

2 RESEARCH QUESTION AND SCOPE

The aim of this project is to compare the clinical effectiveness and safety of satralizumab in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

We followed EUnetHTA guidelines for comparators and comparisons (19), clinical endpoints (20), health related quality of life (21) and safety (22).

Table 2.1: Assessment scope: relevant PICO(s) identified for the planned assessment.

Description	Assessment scope
Population	Patients from 12 years of age with neuromyelitis optica spectrum disorders (NMOSD)[a] who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive
Intervention	• Satralizumab as monotherapy • Satralizumab in combination with immunosuppressive therapy (IST)[b]
Comparison	• Rituximab +/- prednisolone • Azathioprine +/- prednisolone • Mitoxantrone +/- prednisolone • Mycophenolate mofetil +/- prednisolone • Cyclophosphamide • Eculizumab +/- IST • Methotroxate • Tocilizumab • Immunoglobulins

Outcomes	**Clinical effectiveness**
	• Disability progression
	  ○ (eg. Expanded Disability Status Scale (EDSS) Modified Rankin Scale, Auser ambulation index, visual acuity, cognitive impairment)
	• Clinical Relapses
	  ○ (eg. time to first relapse, rate of relapses, total number of relapses)
	• Health related quality of life
	• Imaging biomarkers
	  ○ (eg. brain and spinal cord MRI gad-enhancing lesions, T2 lesions)
	• Symptoms
	  ○ (eg. Fatigue, pain, sphincter dysfunction)
	• Mortality
	
	Safety
	• Treatment related mortality
	• Adverse events leading to treatment discontinuation
	• Serious adverse events
	• Adverse events

[a] ICD11: 8A43; MeSH Terms: NMO Spectrum Disorder; NMO Spectrum Disorders; Neuromyelitis Optica (NMO) Spectrum Disorder; Neuromyelitis Optica Spectrum Disorders; Neuromyelitis Optica (NMO) Spectrum Disorders; Devic Neuromyelitis Optica; Devic Neuromyelitis Opticas; Neuromyelitis Optica, Devic; Neuromyelitis Opticas, Devic; Devic Disease; Disease, Devic; Devic Syndrome; Syndrome, Devic; Devic's Syndrome; Devics Syndrome; Syndrome, Devic's; Devic's Neuromyelitis Optica; Devics Neuromyelitis Optica; Neuromyelitis Optica, Devic's; Neuromyelitis Optica Spectrum Disorder; Devic's Disease; Devics Disease; Disease, Devic's.
[b] We consider any IST deemed necessary in combination with satralizumab (e.g., rituximab, azathioprine plus prednisolone, mitoxantrone, mycophenolate mofetil, cyclophosphamide, or eculizumab)

3 METHODS

As explained in section 1 the finalization of the PTJA13 assessment would occur after the closure of EUnetHTA Joint Action 3, the authoring team was unable to continue this assessment. Therefore, no subsequent work will be carried out. However this chapter reflects the planned methodology if the assessment would have been continued by EUnetHTA.

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process.

3.1 Inclusion criteria

During the assessment the inclusion criteria applied by the pMAH will be checked to evaluate if they capture the PICO defined for the assessment. In addition, the following criteria are considered relevant for study inclusion:

- Study design: Randomized controlled trials

3.2 Information retrieval

The assessment will be based on a Submission Dossier submitted by the pMAH. To allow for a meaningful assessment, the Submission Dossier has to be complete with regard to the available evidence relevant for the research question(s). This requires the systematic identification of all published and unpublished studies relevant to the assessment according to the research question and scope defined in Section 2. The assessment will investigate whether these requirements are met and thus whether the evidence base for the assessment is complete.

The cut-off date for the pMAH's list of sponsored studies and the searches should be a maximum of three months before submission (of the Submission Dossier). This cut-off date will also be relevant for the assessment. There will be no updates of searches beyond this cut-off by the authors of the assessment.

During the assessment, the evidence base with regard to the drug under assessment provided by the pMAH will be reviewed. Search strategies will be checked for appropriateness and the results of information retrieval included in the pMAH's Submission Dossier will be checked for completeness against a search in study registries and against the studies included in the regulatory Assessment Report. If there are major flaws in the search conducted by the pMAH, further supplementary searches, as appropriate, will be conducted to check for possible incompleteness of the study pool. The search date, complete search strategies and the results of these searches will be reported in the assessment.

If the evidence provided in the Submission Dossier is incomplete it will not be supplemented by own searches and analyses by the authors of the assessment. The incompleteness and its consequences for the conclusions of the report will be described in the Assessment Report.

3.3 Data analysis and synthesis

The assessment will be based on the data and analyses included in the Submission Dossier prepared by the pMAH. During the assessment, the completeness of data and analyses in the Submission Dossier will be verified. Furthermore, the methods for data analysis and synthesis applied by the pMAH will be checked against the requirements of the Submission Dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity. The results of this assessment and the results of the included studies, as appropriate, will be presented in the Assessment Report according to the research questions defined in Section 2.

3.3.1 Data extraction

Information used for the assessment of benefits and harms will be extracted from the Submission Dossier and verified against the Clinical Study Reports (CSR) and the Technical Reports on the comparisons of interest or other original documentation provided in the Submission Dossier.

3.3.2 Assessment of risk of bias and certainty of results

The assessment of risk of bias should follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials and non-randomised studies on interventions. The risk of bias of the results of each included study should be described separately for each patient-relevant outcome. For this purpose, risk of bias should be assessed at the study level as well as at the outcome level.

If the outcome-specific risk of bias is classified as high for an outcome, this should not lead to exclusion of the corresponding data. Rather, the risk-of-bias classification should inform the discussion on heterogeneous study results and the determination of certainty of results.

During the assessment, the methods and outcome of the risk-of-bias assessment presented in the Submission Dossier will be evaluated. *Risk-of-bias will be assessed by the authors only for outcomes (and studies) that are included based on the research question(s) (PICO). The result of the risk-of-bias assessment will be presented in the Assessment Report.*

The certainty of results for each comparison will be assessed. For pairwise comparisons (whether using conventional meta-analysis or Bucher ITC), certainty of evidence will include risk of bias, as well as assessment of indirectness, inconsistency, and imprecision, according to the Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodology.

If network meta-analysis is used as a method of comparison, the certainty of evidence will be assessed using the CiNeMA (23)(24)(Confidence in Network Meta-Analysis) method (for frequentist analysis) or using a threshold analysis (25), where possible.

3.3.3 Description of design and results of individual studies

During the assessment, the information in the Submission Dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalization) and study results will be evaluated. The results of this evaluation will be presented, used for identification of relevant analyses and considered for the conclusions of the Assessment Report.

3.3.4 Synthesis of study results

Meta-analyses

If several studies are available for the same PICO, they should be quantitatively pooled in a meta-analysis if they are sufficiently comparable from a clinical (e.g. patient groups) and methodological (e.g. study design) point of view.

During the assessment, the methods applied for the meta-analyses presented in the Submission Dossier, and, if applicable, the justification for deviations from the procedures described above will be evaluated. The meta-analyses relevant for the research questions (see Section 2) will be presented in the Assessment Report.

Sensitivity analyses

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the Submission Dossier and the corresponding methods applied will be evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure. The sensitivity analysis should in particular consider the classification of the risk of bias of study results. The result of the sensitivity analysis can affect the assessment of the certainty of results.

Subgroup analyses and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the Submission Dossier and the corresponding methods applied will be evaluated. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorized. If potential effect modifiers are identified, the conclusions inferred from the effects observed in the complete patient group can possibly be formulated more precisely.

Indirect comparisons

If indirect comparisons are included in the Submission Dossier, the methods applied, and if applicable, the justification in the event of deviations from the required approaches will be evaluated. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the Assessment Report.

3.4 Patient involvement

At the start of this Joint Assessment an open call for patient input was published on the EUnetHTA website. This open call specifically asked patient organisations to answer the questions, as they have the position to collect and present patient's and care-givers' views and experiences by engaging with a wide range of patients and their careers.

The open call used by EUnetHTA asks general questions to elicit patients' views on living with the disease, important outcomes to be considered in this assessment and expectations of a new drug. The questions are based on the HTAi questionnaire template. For more information on the development of the HTAi questionnaire template please see their website.

European and national patient organisations had to provide an organisational perspective on the questions in English. In all parts of the open call, the term 'patient' refers to anyone living with, or who has lived with, the condition for which the new medicine is indicated. One patient organisation completed the survey, namely Asociación Española Síndrome de Sjögren (Spain).

The information gathered from the open call was used to inform the scope of this assessment. The contributions provided are duly incorporated in the Clinical effectiveness outcomes included in the PICO (Table 2.1: Assessment scope: relevant PICO(s) identified for the planned assessment.).

4 PROJECT ORGANISATION

4.1 Participants

Table 4.2: Project participants

Role in the project	Agency	Country	Distribution of work
Assessment Team			
Author	National Authority of Medicines and Health Products (INFARMED)	Portugal	Develop first draft and final version of EUnetHTA project plan with co-author
Co-Author	Erasmus University Rotterdam (EUR) & Dutch National Healthcare Institute (ZIN)	Netherlands	Develop first draft and final version of EUnetHTA project plan with 1st author
Information specialist	National Authority of Medicines and Health Products (INFARMED)	Portugal	Review of information retrieval, conduct of searches required for checking completeness of information retrieval in Submission Dossier; reporting information retrieval check in the Assessment Report
Statistical specialist	National Authority of Medicines and Health Products (INFARMED)	Portugal	Expert review of statistical analyses presented in Submission Dossier, statistical support for authors
Dedicated Reviewer	Healthcare Improvement Scotland (HIS)	Scotland	
Dedicated Reviewer	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	Slovenia	
Dedicated Reviewer	Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	Spain	
Contributors			
Patient organisations	Asociación Española Síndrome de Sjögren	Spain	Complete the EUnetHTA open call in order to inform the scope of the assessment
Project Manager	Zorginstituut Nederland (ZIN)	Netherlands	Coordination between involved parties throughout the assessment period

4.2 Project stakeholders

Table 3.2: Project stakeholders

Organisation	Role in the project
Roche	Manufacturer (MAH) Completing the Submission Dossier[1]; Fact check of the draft Assessment Report[1];.

4.3 Milestones and deliverables

Table 4.3: Milestones and deliverables

Milestones/Deliverables	Start date	End date
Project duration	**20-08-2019**	**28-04-2021**
Letter of Intent received	20-08-2019	
Scoping phase	**04-10-2019**	**26-03-2020**
Scoping PICO and development of first draft Project Plan	04-10-2019	11-11-2019
PICO survey – request relevant PICO from Member States	14-10-2019	24-10-2019
Adapt draft Project Plan based on PICO survey	29-10-2019	11-11-2019
Open call for patient input	16-10-2019	07-05-2020
Review of first draft Project Plan	12-11-2019	21-11-2019
Development of second draft Project Plan & answers to DR comments	22-11-2019	04-12-2019
Receive Scoping F2F meeting documents from pMAH	22-11-2019	
Pre-scoping e-meeting with the Assessment Team	10-12-2019	
Share discussion topics for Scoping F2F Meeting	13-05-2020	
Scoping F2F meeting with manufacturer	20-05-2020	
Share action points from F2F meeting with manufacturer	27-05-2020	
Receive Submission Dossier from pMAH[1]	NA	
CHMP opinion	*22-04-2021*	
Finalize Project Plan	*28-04-2021*	
Discontinuation of the assessment	*28-04-2021*	

[1] Given the circumstances described in Section 1, these activities were not performed.

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